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<p>(21) International Application Number: PCT/US96/12661</p> <p>(22) International Filing Date: 2 August 1996 (02.08.96)</p> <p>(30) Priority Data: 60/001,792 2 August 1995 (02.08.95) US 60/010,982 1 February 1996 (01.02.96) US </p> <p>(71) Applicant (<i>for all designated States except US</i>): SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): LUENGO, Juan Ignacio [ES/US]; 701 Pondview Drive, Audubon, PA 19403 (US). ELLIOTT, John, Duncan [GB/US]; 723 Old Eagle School Road, Wayne, PA 19087 (US). XIANG, Jia-Ning [CN/US]; 306 Danor Court, Wayne, PA 19087 (US).</p> <p>(74) Agents: HALL, Linda, E. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).</p>		<p>(81) Designated States: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>	
<p>(54) Title: ENDOTHELIN RECEPTOR ANTAGONISTS</p> <p>(57) Abstract</p> <p>Novel pyrroles, pyrazoles and triazoles, pharmaceutical compositions containing these compounds and their use as endothelin receptor antagonists are described.</p>			

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ENDOTHELIN RECEPTOR ANTAGONISTSFIELD OF INVENTION

- The present invention relates to novel pyrroles, pyrazoles and triazoles,
5 pharmaceutical compositions containing these compounds and their use as
endothelin receptor antagonists.

Endothelin (ET) is a highly potent vasoconstrictor peptide synthesized and released by the vascular endothelium. Endothelin exists as three isoforms, ET-1, ET-2 and ET-3. [Unless otherwise stated "endothelin" shall mean any or all of the 10 isoforms of endothelin]. Endothelin has profound effects on the cardiovascular system, and in particular, the coronary, renal and cerebral circulation. Elevated or abnormal release of endothelin is associated with smooth muscle contraction which is involved in the pathogenesis of cardiovascular, cerebrovascular, respiratory and renal pathophysiology. Elevated levels of endothelin have been reported in plasma 15 from patients with essential hypertension, acute myocardial infarction, subarachnoid hemorrhage, atherosclerosis, and patients with uraemia undergoing dialysis.

In vivo, endothelin has pronounced effects on blood pressure and cardiac output. An intravenous bolus injection of ET (0.1 to 3 nmol/kg) in rats causes a transient, dose-related depressor response (lasting 0.5 to 2 minutes) followed by a 20 sustained, dose-dependent rise in arterial blood pressure which can remain elevated for 2 to 3 hours following dosing. Doses above 3 nmol/kg in a rat often prove fatal.

Endothelin appears to produce a preferential effect in the renal vascular bed. It produces a marked, long-lasting decrease in renal blood flow, accompanied by a significant decrease in GFR, urine volume, urinary sodium and potassium excretion. 25 Endothelin produces a sustained antinatriuretic effect, despite significant elevations in atrial natriuretic peptide. Endothelin also stimulates plasma renin activity. These findings suggest that ET is involved in the regulation of renal function and is involved in a variety of renal disorders including acute renal failure, cyclosporine nephrotoxicity, radio contrast induced renal failure and chronic renal failure.

Studies have shown that in vivo, the cerebral vasculature is highly sensitive to both the vasodilator and vasoconstrictor effects of endothelin. Therefore, ET may be an important mediator of cerebral vasospasm, a frequent and often fatal consequence of subarachnoid hemorrhage.

5 ET also exhibits direct central nervous system effects such as severe apnea and ischemic lesions which suggests that ET may contribute to the development of cerebral infarcts and neuronal death.

ET has also been implicated in myocardial ischemia (Nichols et al. Br. J. Pharm. 99: 597-601, 1989 and Clozel and Clozel, Circ. Res., 65: 1193-1200, 1989) 10 coronary vasospasm (Fukuda et al., Eur. J. Pharm. 165: 301-304, 1989 and Lüscher, Circ. 83: 701, 1991) heart failure, proliferation of vascular smooth muscle cells, (Takagi, Biochem & Biophys. Res. Commun.; 168: 537-543, 1990, Bobek et al., Am. J. Physiol. 258:408-C415, 1990) and atherosclerosis, (Nakaki et al., Biochem. & Biophys. Res. Commun. 158: 880-881, 1989, and Lerman et al., New Eng. J. of Med. 325: 997-1001, 1991). Increased levels of endothelin have been shown after 15 coronary balloon angioplasty (Kadel et al., No. 2491 Circ. 82: 627, 1990).

Further, endothelin has been found to be a potent constrictor of isolated mammalian airway tissue including human bronchus (Uchida et al., Eur J. of Pharm. 154: 227-228 1988, LaGente, Clin. Exp. Allergy 20: 343-348, 1990; and 20 Springall et al., Lancet, 337: 697-701, 1991). Endothelin may play a role in the pathogenesis of interstitial pulmonary fibrosis and associated pulmonary hypertension, Glard et al., Third International Conference on Endothelin, 1993, p. 34 and ARDS (Adult Respiratory Distress Syndrome), Sanai et al., Supra, p. 112.

Endothelin has been associated with the induction of hemorrhagic and 25 necrotic damage in the gastric mucosa (Whittle et al., Br. J. Pharm. 95: 1011-1013, 1988); Raynaud's phenomenon, Cinniniello et al., Lancet 337: 114-115, 1991); Crohn's Disease and ulcerative colitis, Munch et al., Lancet, Vol. 339, p. 381; Migraine (Edmeads, Headache, Feb. 1991 p 127); Sepsis (Weitzberg et al., Circ. Shock 33: 222-227, 1991; Pittet et al., Ann. Surg. 213: 262-264, 1991), 30 Cyclosporin-induced renal failure or hypertension (Eur. J. Pharmacol., 180: 191-192, 1990, Kidney Int., 37: 1487-1491, 1990) and endotoxin shock and other

endotoxin induced diseases (Biochem. Biophys. Res. Commun., 161: 1220-1227, 1989, Acta Physiol. Scand. 137: 317-318, 1989) and inflammatory skin diseases. (Clin. Res. 41:451 and 484, 1993).

Endothelin has also been implicated in preclampsia of pregnancy. Clark et al., Am. J. Obstet. Gynecol. March 1992, p. 962-968; Kamor et al., N. Eng. J. of Med., Nov 22, 1990, p. 1486-1487; Dekker et al., Eur. J. Ob. and Gyn. and Rep. Bio. 40 (1991) 215-220; Schiff et al., Am. J. Obstet. Gynecol. Feb 1992, p. 624-628; diabetes mellitus, Takahashi et al., Diabetologia (1990) 33:306-310; and acute vascular rejection following kidney transplant, Watschinger et al., Transplantation 10 Vol. 52, No. 4, pp. 743-746.

Endothelin stimulates both bone resorption and anabolism and may have a role in the coupling of bone remodeling. Tatrai et al. Endocrinology, Vol. 131, p. 603-607.

Endothelin has been reported to stimulate the transport of sperm in the uterine cavity, Casey et al., J. Clin. Endo and Metabolism, Vol. 74, No. 1, p. 223-225, therefore endothelin antagonists may be useful as male contraceptives. Endothelin modulates the ovarian/menstrual cycle, Kenegsberg, J. of Clin. Endo. and Met., Vol. 74, No. 1, p. 12, and may also play a role in the regulation of penile vascular tone in man, Lau et al., Asia Pacific J. of Pharm., 1991, 6:287-292 and Tejada et al., J. Amer. Physio. Soc. 1991, H1078-H1085. Endothelin also mediates a potent contraction of human prostatic smooth muscle, Langenstroer et al., J. Urology, Vol. 149, p. 495-499.

Thus, endothelin receptor antagonists would offer a unique approach toward the pharmacotherapy of hypertension, acute and chronic renal failure, ischemia induced renal failure, sepsis-endotoxin induced renal failure, prophylaxis and/or treatment of radio-contrast induced renal failure, acute and chronic cyclosporin induced renal failure, cerebrovascular disease, cerebrovascular spasm, subarachnoid hemorrhage, myocardial ischemia, angina, congestive heart failure, acute coronary syndrome, myocardial salvage, unstable angina, asthma, primary pulmonary hypertension, pulmonary hypertension secondary to intrinsic pulmonary disease, atherosclerosis, Raynaud's phenomenon, ulcers, sepsis, migraine, glaucoma,

endotoxin shock, endotoxin induced multiple organ failure or disseminated intravascular coagulation, cyclosporin-induced renal failure and as an adjunct in angioplasty for prevention of restenosis, diabetes, diabetic retinopathy, retinopathy, diabetic nephropathy, diabetic macrovascular disease, atherosclerosis, preclampsia
5 of pregnancy, bone remodeling, kidney transplant, male contraceptives, infertility and priapism and benign prostatic hypertrophy.

SUMMARY OF THE INVENTION

This invention comprises compounds represented by Formula (I) and
10 pharmaceutical compositions containing these compounds, and their use as endothelin receptor antagonists which are useful in the treatment of a variety of cardiovascular and renal diseases including but not limited to: hypertension, acute and chronic renal failure, cyclosporine induced nephrotoxicity, benign prostatic hypertrophy, pulmonary hypertension, migraine, stroke, subarachnoid hemorrhage,
15 cerebrovascular vasospasm, myocardial ischemia, angina, congestive heart failure, atherosclerosis, diabetic nephropathy, diabetic retinopathy, retinopathy, diabetic macrovascular disease, atherosclerosis and as an adjunct in angioplasty for prevention of restenosis.

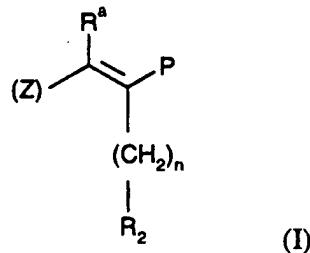
This invention further constitutes a method for antagonizing endothelin
20 receptors in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of Formula (I).

This invention also constitutes intermediates represented by Formula (II). In a further aspect the present invention provides a process for the preparation of a compound of Formula (I)(d).

DETAILED DESCRIPTION OF THE INVENTION

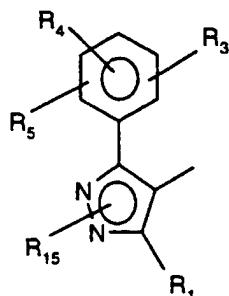
The compounds of this invention are represented by structural Formula (I):

5

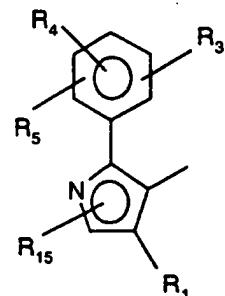


wherein (Z) is

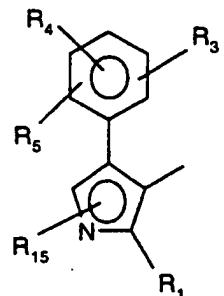
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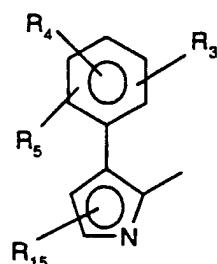
(d)



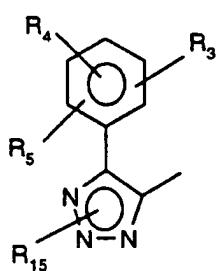
(e)



(f)

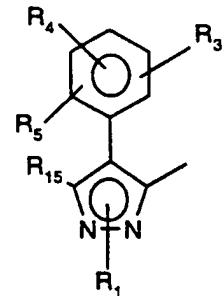


(g)

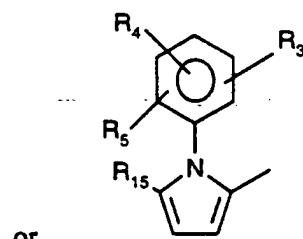


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(h)



(i)



(j)

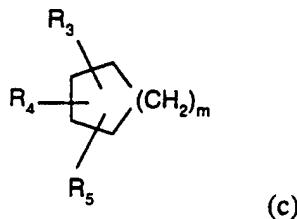
P is tetrazol-5-yl, CO_2R_6 or $\text{C}(\text{O})\text{N}(\text{R}_6)\text{S}(\text{O})_q\text{R}_{10}$;

R^a is independently hydrogen or $\text{C}_{1-6}\text{alkyl}$;

R_1 is independently hydrogen, Ar, $\text{C}_{1-6}\text{alkyl}$ or C_{1-6} alkoxy;

R_2 is Ar, $\text{C}_{1-8}\text{alkyl}$, $\text{C}(\text{O})\text{R}_{14}$ or

5



R_3 and R_5 are independently R_{13}OH , $\text{C}_{1-8}\text{alkoxy}$, $\text{S}(\text{O})_q\text{R}_{11}$, $\text{N}(\text{R}_6)_2$, NO_2 , Br, F, I, Cl, CF_3 , NHCOR_6 , $\text{R}_{13}\text{CO}_2\text{R}_7$, $-\text{X}-\text{R}_9-\text{Y}$, $-\text{X}(\text{C}(\text{R}_6)_2)\text{OR}_6$, $-(\text{CH}_2)_m\text{X}'\text{R}_8$ or -

10 $\text{X}(\text{CH}_2)_n\text{R}_8$ wherein each methylene group within $-\text{X}(\text{CH}_2)_n\text{R}_8$ may be unsubstituted or substituted by one or two $-(\text{CH}_2)_n\text{Ar}$ groups;

R_4 is independently R_{11} , OH, $\text{C}_{1-5}\text{alkoxy}$, $\text{S}(\text{O})_q\text{R}_{11}$, $\text{N}(\text{R}_6)_2$, Br, F, I, Cl or NHCOR_6 , wherein the $\text{C}_{1-5}\text{alkoxy}$ may be unsubstituted or substituted by OH, methoxy or halogen;

15 R_6 is independently hydrogen or $\text{C}_{1-8}\text{alkyl}$;

R_7 is independently hydrogen, $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$ or $\text{C}_{2-8}\text{alkynyl}$, all of which may be unsubstituted or substituted by one or more OH, $\text{N}(\text{R}_6)_2$, CO_2R_{12} , halogen or $\text{XC}_{1-10}\text{alkyl}$; or R_7 is $(\text{CH}_2)_n\text{Ar}$;

R_8 is independently R_{11} , CO_2R_7 , $\text{CO}_2\text{C}(\text{R}_{11})_2\text{O}(\text{CO})\text{XR}_7$, $\text{PO}_3(\text{R}_7)_2$, $\text{SO}_2\text{NR}_7\text{R}_{11}$,

20 $\text{NR}_7\text{SO}_2\text{R}_{11}$, $\text{CONR}_7\text{SO}_2\text{R}_{11}$, SO_3R_7 , SO_2R_7 , $\text{P}(\text{O})(\text{OR}_7)\text{R}_7$, CN,

$\text{CO}_2(\text{CH}_2)_m\text{C}(\text{O})\text{N}(\text{R}_6)_2$, $\text{C}(\text{R}_{11})_2\text{N}(\text{R}_7)_2$, $\text{C}(\text{O})\text{N}(\text{R}_6)_2$, $\text{NR}_7\text{C}(\text{O})\text{NR}_7\text{SO}_2\text{R}_{11}$,

OR₆, or tetrazole which is substituted or unsubstituted by $\text{C}_{1-6}\text{alkyl}$;

R_9 is independently a bond, $\text{C}_{1-10}\text{alkylene}$, $\text{C}_{1-10}\text{alkenylene}$, $\text{C}_{1-10}\text{alkylidene}$, $\text{C}_{1-10}\text{alkynylene}$, all of which may be linear or branched, or phenylene, all of which may

25 be unsubstituted or substituted by one or more OH, $\text{N}(\text{R}_6)_2$, COOH or halogen;

R_{10} is independently $\text{C}_{1-10}\text{alkyl}$, $\text{N}(\text{R}_6)_2$ or Ar;

R_{11} is independently hydrogen, Ar, $\text{C}_{1-8}\text{alkyl}$, $\text{C}_{2-8}\text{alkenyl}$, $\text{C}_{2-8}\text{alkynyl}$, all of which may be unsubstituted or substituted by one or more OH, CH_2OH , $\text{N}(\text{R}_6)_2$ or halogen;

R₁₂ is independently hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₇alkynyl;

R₁₃ is independently divalent Ar, C₁₋₁₀alkylene, C₁₋₁₀alkylidene, C₂₋₁₀alkenylene, all of which may be unsubstituted or substituted by one or two OH, CH₂OH, N(R₆)₂ or halogen;

5 R₁₄ is independently hydrogen, C₁₋₁₀alkyl, XC₁₋₁₀alkyl, Ar or XAr;

R₁₅ is independently hydrogen, Ar, C₁₋₆alkyl, or XAr;

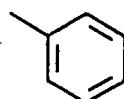
R₁₆ is independently C₁₋₆alkyl or phenyl substituted by one or two C₁₋₆alkyl, OH, C₁₋₅alkoxy, S(O)_qR₆, N(R₆)₂, Br, F, I, Cl, CF₃ or NHCOR₆;

X is independently (CH₂)_n, O, NR₆ or S(O)_q;

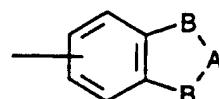
10 X' is independently O, NR₆ or S(O)_q;

Y is independently CH₃ or X(CH₂)_nAr;

Ar is:



(a)



(b)

15

naphthyl, indolyl, pyridyl, thienyl, oxazolidinyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, or pyrimidyl; all of
20 which may be unsubstituted or substituted by one or two Z₁ or Z₂ groups;

A is independently C=O, or (C(R₆)₂)_m;

B is independently -CH₂- or -O-;

Z₁ and Z₂ are independently hydrogen, XR₆, C₁₋₈alkyl, (CH₂)_qCO₂R₆, C(O)N(R₆)₂,

25 CN, (CH₂)_nOH, NO₂, F, Cl, Br, I, N(R₆)₂, NHC(O)R₆, O(CH₂)_mC(O)NR_aSO₂R₁₆, (CH₂)_mOC(O)NR_aSO₂R₁₆, O(CH₂)_mNR_aC(O)NR_aSO₂R₁₆ or tetrazolyl which may be substituted or unsubstituted by one or two C₁₋₆alkyl, CF₃ or C(O)R₆;

m is independently 1 to 3;

n is independently 0 to 6;

30 q is independently 0, 1 or 2;

provided R₃, R₄ and R₅ are not O-O(CH₂)_nAr;
and further provided that R₂ is not dihydrobenzofuran;
or a pharmaceutically acceptable salt thereof.

All alkyl, alkenyl, alkynyl and alkoxy groups may be straight or branched.

5 Halogen may be Br, Cl, F or I.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active form. All of these compounds and diastereoisomers are contemplated to be within the scope of the present invention.

10 Preferred compounds are those wherein:

P is CO₂R₆; more preferably P is CO₂H.

R₁ is hydrogen.

15

R₂ is Ar, cyclohexyl or C₁₋₄alkyl. More preferably R₂ is a group Ar wherein Ar is a group (a) or (b). In said group (a) or (b) Z₁ and Z₂ are independently hydrogen, CO₂R₆, (CH₂)_nOH, C₁₋₄alkyl or C₁₋₆ alkoxy, e.g. methoxy; A is preferably CH₂, both Bs are preferably O.

20

R₃ and R₅ are independently hydrogen, CO₂R₆, OH, C₁₋₈alkoxy, C₁₋₈alkyl, N(R₆)₂, NO₂, Br, F, Cl, I, R₁₃CO₂R₇, X(CH₂)_nR₈, (CH₂)_mX'R₈, or X(C(R₆)₂)_mOR₆;

25

In the context of the group R₃ and R₅ preferably do not represent hydrogen. In particular in the group R₃ preferably represents Br, Cl, C₁₋₈alkoxy e.g. methoxy; X(CH₂)_nR₈, wherein X preferably represents O, n is 0, 1, or 2, and R₈ is preferably selected from:

CO₂R₆ wherein R₆ is preferably hydrogen;

30 OR₆ wherein R₆ is preferably H;

- tetrazolyl optionally substituted by C₁-galkyl e.g. ethyl; CONR₇SO₂R₁₁ wherein R₇ is H or C₁-galkyl e.g. methyl, R₁₁ preferably is C₁-galkyl (e.g. methyl, isopropyl, or t-butyl) or phenyl optionally substituted by Br, Cl, F, C₁-galkyl e.g. methyl;
- 5 or R₈ is phenyl or pyridyl substituted by one or more Br, Cl, CO₂H, CH₂OH.

R₅ is C₁-galkoxy e.g. methoxy, or N(R₆)₂ wherein R₆ preferably is H or methyl.

- 10 R₄ is hydrogen, OH, C₁-5alkoxy, N(R₆)₂, Br, F, Cl, I, NHCOCH₃, or S(O)_q C₁-5alkyl wherein the C₁-5alkyl may be unsubstituted or substituted by OH, methoxy or halogen. R₄ is more preferably hydrogen;

R₆ is hydrogen or C₁-galkyl e.g. methyl and ethyl;

- 15 R₇ is hydrogen, C₁-10alkyl, C₂-10alkenyl or C₂-galkynyl, all of which may be unsubstituted or substituted by one or more OH, N(R₆)₂, CO₂R₁₂, halogen, or R₇ is (CH₂)_nAr. When R₇ is (CH₂)_nAr, n is preferably zero or 1 and Ar is preferably phenyl substituted or unsubstituted by halogen or C₁-5 alkoxy.

- 20 R₁₁ is hydrogen, phenyl, pyridyl wherein the phenyl and pyridyl may be substituted or unsubstituted by one or two C₁-4alkyl groups; C₁-galkyl, C₂-galkenyl, C₂-galkynyl, all of which may be substituted or unsubstituted by one or more OH, CH₂OH, N(R₆)₂, or halogen;

- 25 R₁₂ is hydrogen or C₁-6alkyl.

R₁₃ is phenyl, pyridyl, or C₂-10alkylene, all of which may be unsubstituted or substituted by one or more CO₂R₆, OH, CH₂OH, N(R₆)₂, or halogen;

- 30 R₁₅ is preferably hydrogen or C₁-6alkyl e.g. ethyl, isopropyl, n-butyl, cyclopropylmethyl or cyclopropylethyl.

(Z) is preferably (d).

Preferred compounds are:

5 (E)-alpha-[[1-Butyl-5-[2-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid;

(E)-alpha-[[5-[2-[(2-Carboxyphenyl)methoxy]-4-methoxyphenyl]-1-ethyl-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid;

10 (E)-alpha-[[1-Allyl-5-[2-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid;

15 (E)-alpha-[[1-Butyl-5-[2-[(2-carboxyphenyl)methoxy]-4-chlorophenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid;

(E)-alpha-[[1-Butyl-5-[4-methoxy-2-[[N-(phenylsulfonyl)]carboxamidomethoxy]phenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid;

20 (E)-3-[1-Butyl-5-[2-[2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(2,5-dimethoxyphenyl)methyl]-prop-2-enoic acid;

25 (E)-alpha-[[1-Butyl-5-[2-[(2-hydroxymethylphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid;

(E)-alpha-[[1-Butyl-5-[2-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-7-methoxy-1,4-benzodioxan-6-propanoic acid;

(E)-alpha-[[5-[2-[(2-Carboxyphenyl)methoxy]-4-methoxyphenyl]-1-cyclopropylmethyl-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid;

5 (E)-alpha-[[1-(3-Butenyl)-5-[2-[(2-hydroxymethylphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid;

10 (E)-alpha-[[5-[2-[(2-Carboxyphenyl)methoxy]-4-methoxyphenyl]-1-cyclopropylethyl-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid;

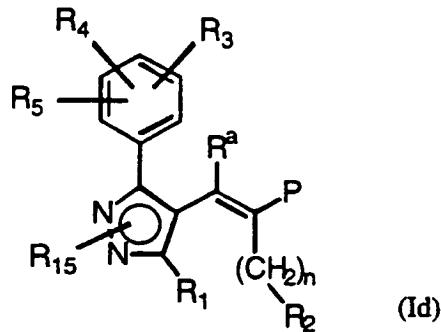
(E)-alpha-[[1-Butyl-5-[2-[(2-carboxyphenoxy)methyl]-4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid.

15

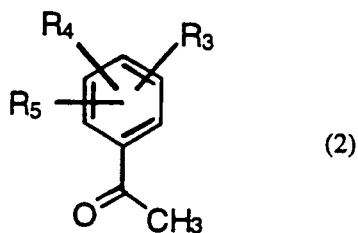
The present invention provides compounds of Formula (I), which may be made by methods similar to those given below.

Compounds of the Formula (Id)

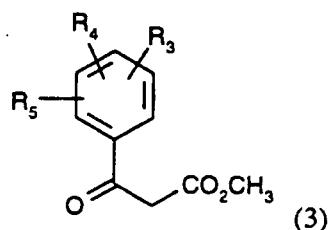
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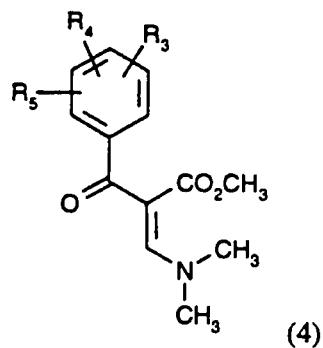
can be prepared by alkylating a ketone of Formula (2)



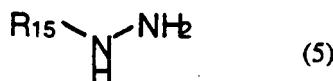
- 5 in dimethyl carbonate in the presence of sodium hydride to provide a β -keto ester of Formula (3).



- Condensation of a β -keto ester of Formula (3) with dimethyl formate dimethyl acetal
10 in a suitable solvent such as toluene at approximately 95 °C affords a compound of Formula (4).

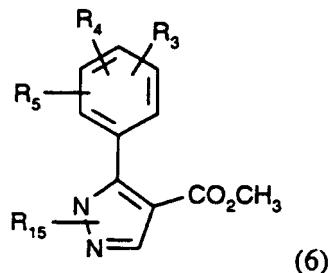


Treatment of a compound of Formula (4) with a hydrazine derivative of the Formula (5)



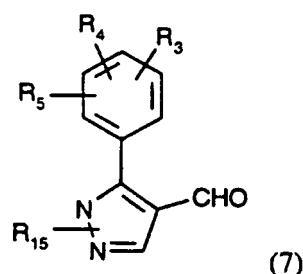
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wherein R₁₅ is C₁₋₆alkyl;
in suitable solvents such as methanol and water in the presence of sodium acetate
provides a pyrazole of Formula (6).

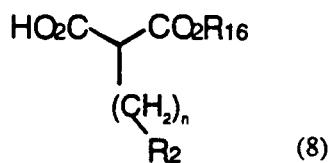


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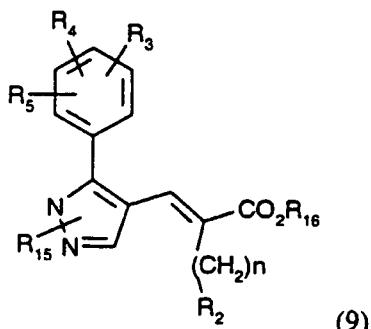
Reduction of an ester of Formula (6) with a reducing agent such as diisobutylaluminum hydride in a solvent such as dichloromethane followed by oxidation with an oxidant such as Jones reagent in acetone affords an aldehyde of
15 Formula (7).



Knoevenagel condensation of an aldehyde of Formula (7) with a half acid of Formula (8), wherein R₁₆ is C₁₋₈ alkyl



- 5 in a solvent such as benzene at reflux, in the presence of piperidinium acetate with azeotropic removal of water using a Dean-Stark apparatus to afford an ester of Formula (9).



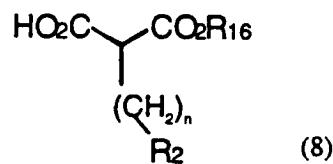
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Followed if necessary and desired by:

- 1) deprotection and alkylation and hydrolysis of the R₃, R₄, R₅, R₁₅, R₁₆, Z₁ and Z₂ groups as required and;
 - 2) salt formation.
- 15 Aldehyde condensation may also be effectuated by heating in the presence of pyridine and acetic acid.

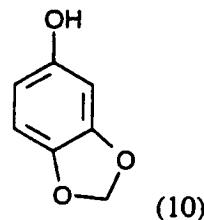
Conversion of an ester of formula (9) into an acid may be carried out using conventional deprotection techniques and hydrolysis.

A half acid of Formula (8),



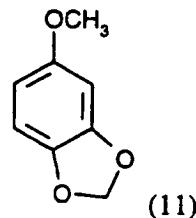
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Wherein n=1, R₂ is (b), A=CH₂, B=O and R₁₆ is C₁₋₆ alkyl, may be prepared by reacting a compound of Formula (10)



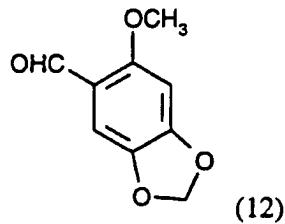
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with methyl iodide in the presence of sodium hydride in a solvent such as dimethyl formamide to provide a compound of Formula (11).



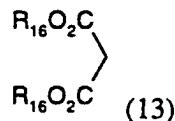
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Treatment of a compound of Formula (11) with POCl_3 in dimethyl formamide affords an aldehyde of Formula (12).



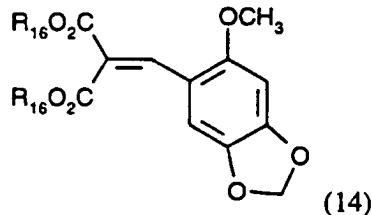
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Condensation of an aldehyde of Formula (12) with a dialkyl malonate of Formula (13)



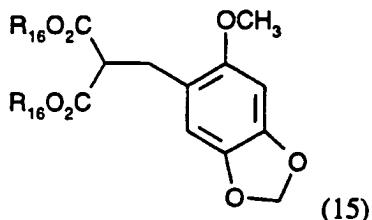
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in the presence of piperidine and acetic acid in benzene provides a α,β -unsaturated ester of Formula (14).



15

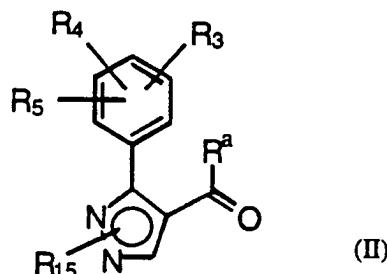
Reduction of a α,β -unsaturated ester of Formula (14) with sodium borohydride in a solvent such as ethanol gives a compound of Formula of (15)



Monosaponification of a diester of Formula (15) with a base such as potassium hydroxide in a mixture of ethanol and water followed by acidic work up provides a half acid of Formula (8).

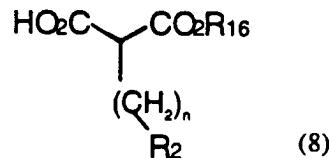
- 5 Other compounds of formula (Id) may be prepared by methods well known in the art. The invention also is a process for preparing compounds of Formula (Id) by:

- (a) Reaction of a compound of Formula (II)



10

or a protected form or precursor thereof (as defined hereinafter) with a compound of Formula (8)



15

(wherein R₂ and R₁₆ are as defined for Formula (Id) hereinabove);

followed if necessary or desired by:

- (b) conversion of one compound of Formula (Id) into a different compound of
20 Formula (Id) e.g.

(i) when Formula (Id) contains a group CO₂R₆, CO₂R₇ or CO₂R₁₂
wherein R₆, R₇ or R₁₂ is alkyl, conversion to a corresponding compound where
R₆, R₇ or R₁₂ represents hydrogen;

(ii) when Formula (Id) contains a hydroxy group (e.g. in R₃, R₄ or R₅) conversion to a different group, e.g. a group (CH₂)Ar where Ar is optionally substituted phenyl, by method well known in the art; and/or
 (c) salt formation.

5

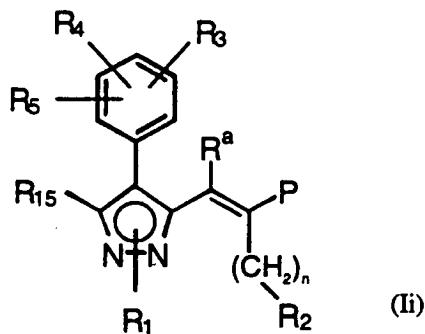
It will be appreciated by those skilled in the art that the substitutents R₃, R₄, R₅, R₁₅ and Z₁ and Z₂ may be introduced at any appropriate stage of the synthesis, preferably at an early stage, using methods well known in the art. In some of the reactions depicted above, particularly those in the early stages of the overall

10 synthesis, one or more of the substitutents may therefore represent a precursor for the eventual substituent. A precursor for any of the substitutents means a group which may be derivatised or converted into the desired group. It will be further appreciated that it may be necessary or desirable to protect certain of these substitutents(or their precursors) at various stages in the reaction sequence. Suitable
 15 precursors and protecting groups are well known to those skilled in the art, as are methods for their conversion or removal respectively.

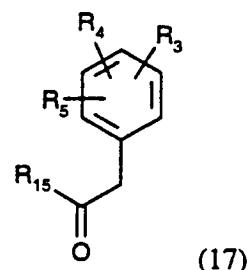
In another aspect the invention provides for an intermediate of the formula (II) wherein R₁₅, R₃, R₄, R₅ and R^a are as described for Formula (I)

20

Compounds of Formula (II)

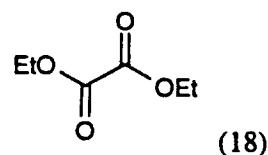


can be prepared starting by commercially available ketones of Formula (17)

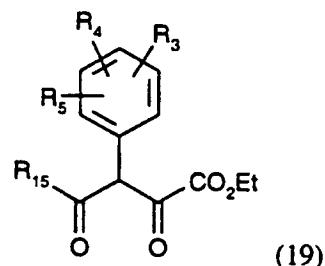


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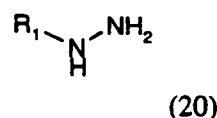
by reaction with diethyl oxalate of Formula (18)



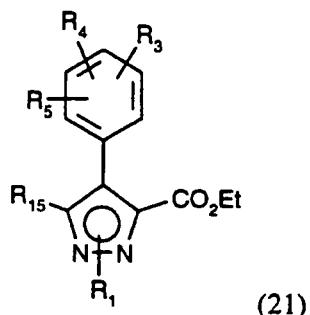
- 10 in the presence of a base such as sodium ethoxide in a solvent such as ethanol to produce a diketone of Formula (19).



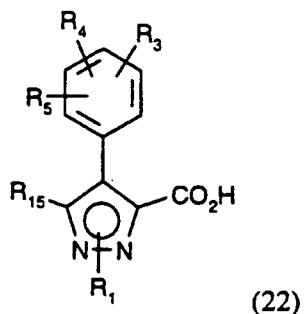
- 15 Reaction of a diketone of Formula (19) with hydrazine derivative of Formula (20)



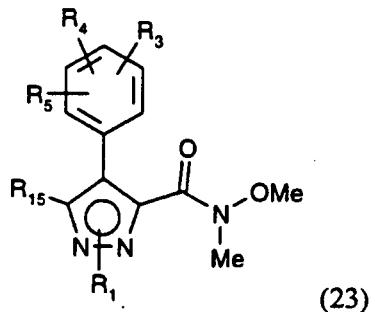
in a suitable solvent such as ethanol at reflux provides a pyrazole of Formula (21).



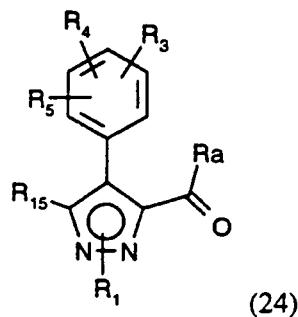
- 5 Saponification of an ester of Formula (21) using lithium hydroxide in a solvent such as aqueous methanol affords, after acidification an acid of the Formula (22),



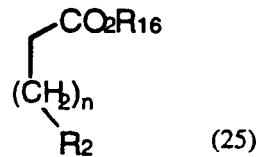
- 10 which can be subsequently converted to the corresponding N-methoxy-N-methylamide of Formula (23)



by treatment with methyl chloroformate followed by N,O-dimethylhydroxylamine hydrochloride in the presence of a base such as N-methylpiperidine. Compound of Formula (23) can be treated with an organometallic reagent Ra-M wherein Ra is C₁₋₆ alkyl and m is Li or MgCl; to provide a compound of Formula (24), wherein Ra is C₁₋₆alkyl.

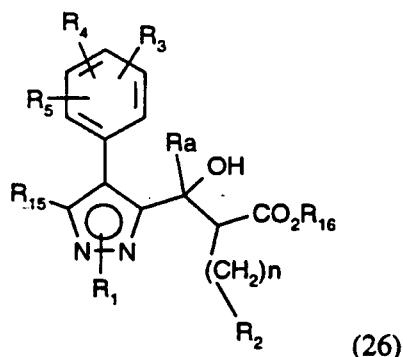


Reaction of compound of Formula (24) with the the lithium enolate of an ester of
10 Formula (25)



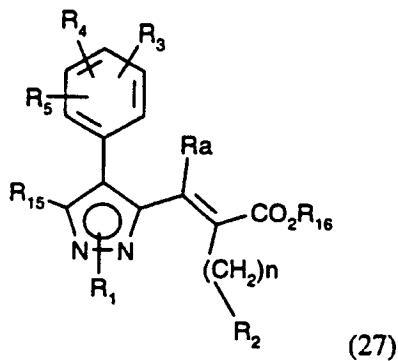
provides an alcohol of Formula (26)

15



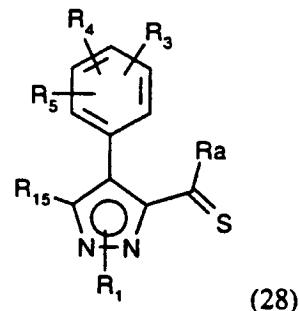
Dehydration of compound of Formula (26) with acetic anhydride followed by treatment with a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene provides a compound of Formula (27)

5



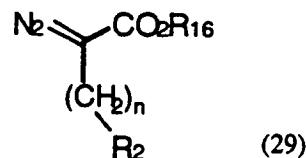
Alternatively, reaction of compound (24), wherein R^a is C₁₋₆alkyl, with Lawesson's reagent in a suitable solvent such as tetrahydrofuran affords a thione of Formula (28),

10

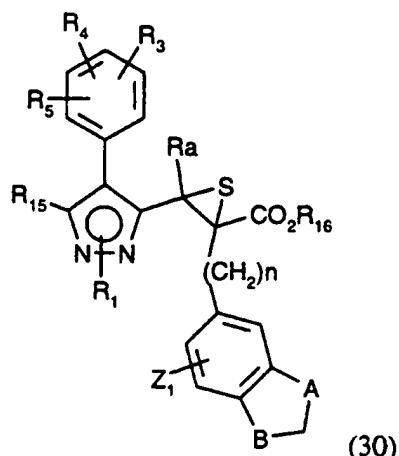


which can be treated with diazoester (29)

15



in refluxing tetrahydrofuran to provide a thiirane of Formula (30).

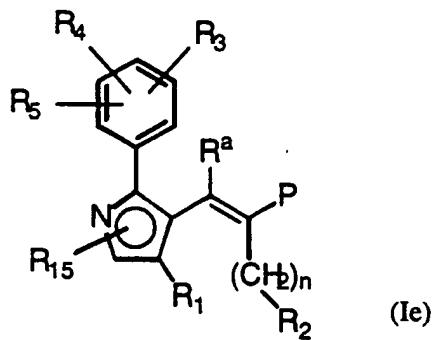


- 5 Treatment of a thiirane of Formula (30) with trimethylphosphite at reflux in a solvent such as chloroform provides compounds of Formula (27), wherein R^a is C₁₋₆alkyl.

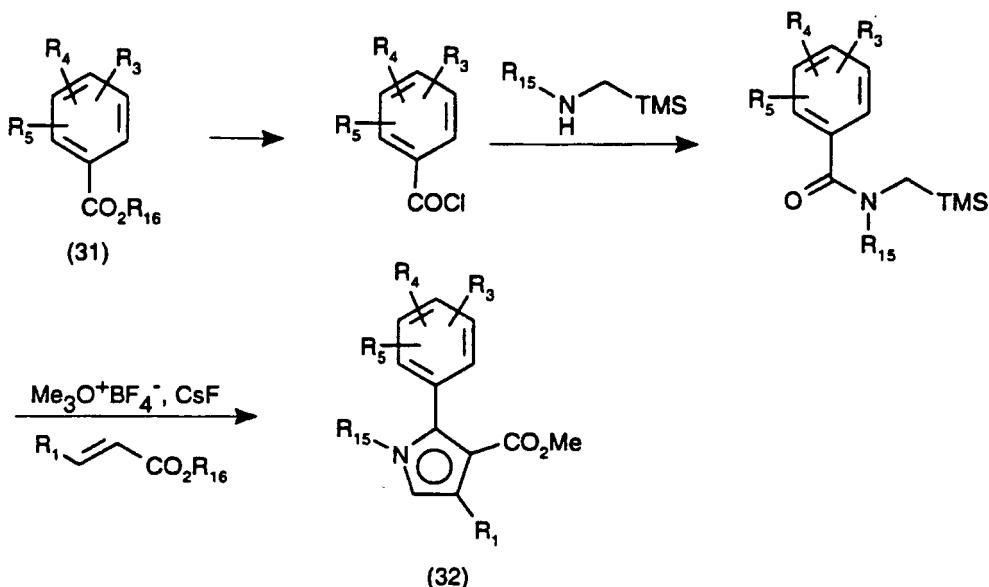
- 10 Saponification of an ester of Formula (27) using lithium hydroxide in a solvent such as aqueous methanol affords, after acidification with acetic acid, an acid of the Formula (Ii), wherein P is CO₂H.

Compounds of the Formula (Ie)

15



can be prepared following the steps outlined in the following Scheme



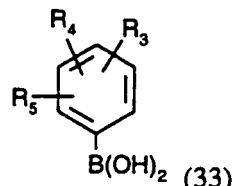
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starting from an aryl ester of Formula (31), wherein R₁₆ is C₁₋₈ alkyl, to provide a pyrrole of Formula (32). Compound of Formula (32) can be subsequently converted to compounds of Formula (Ie) following the same sequence of steps as the one described above for the conversions of compound (6) and compound (21) to

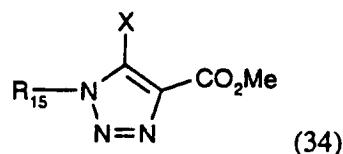
10 compounds (Id) and compound (Ii), respectively.

Compounds of Formula (Ih) may be prepared starting from a boronic acid of Formula (33)

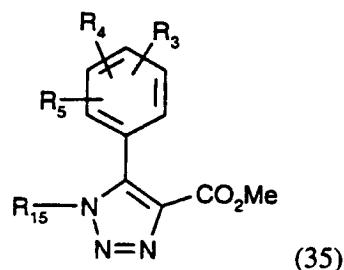
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with a triazole of Formula (34), wherein X is Cr or Br;

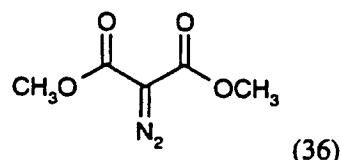


5 under standard Suzuki coupling conditions to provide an ester of Formula (35)



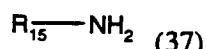
A compound of Formula (33) may be prepared by reaction of a corresponding
10 organometallic derivative (eg lithium or Grignard) with a trialkyl borate followed by hydrolysis.

A compound of Formula (34) may be prepared starting from dimethyl malonate with p-acetaminobenzenesulfonyl azide in a solvent such as acetonitrile in the of a base
15 such as triethyl amine to provide dimethyl diazomalonate (36).

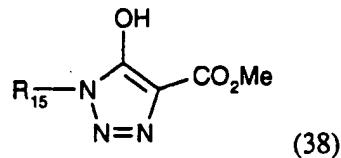


Treatment of diazomalonate of Formula (36) with an amine of Formula (37)

20

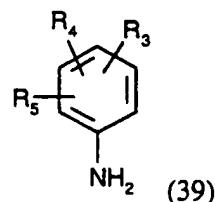


followed by acidic work up provides a triazole of Formula (38)

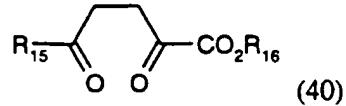


- 5 Reaction of a compound of Formula (38) with PX_5 , whereas X is Br or Cl, in the presence of potassium carbonate in dimethylformamide affords a compound of Formula (34).

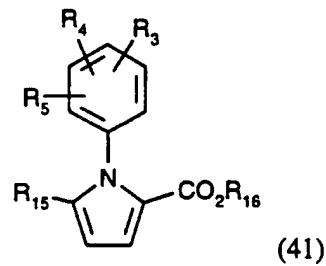
Compounds of Formula (Ij) may be prepared starting from an analine of Formula
10 (39)



with a diketone of Formula (40)
15

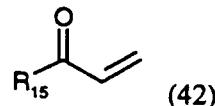


in a suitable solvent such as ethyl alcohol at reflux to provide a pyrrole of Formula
20 (41).

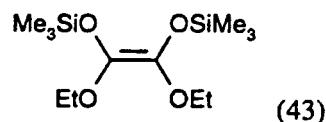


A diketone of Formula of (40) might be prepared by reacting of α,β -unsaturated ketone of Formula (42)

5



with a silyl enol ether of Formula (43)



10

in the presence of Lewis acid such as zinc chloride in a suitable solvent such as dichloromethane followed by acidic hydrolysis.

Compounds of Formula (35) and compounds of Formula (41) can be subsequently
15 converted to compounds of Formula (Ih) and compounds of Formula (Ij),
respectively, following the same sequence of steps as the one described above for the
conversions of compound (6), compound (21) and compound (32) to compounds
(Id), compound (Ii) and compound (Ie), respectively.

In order to use a compound of the Formula (I) or a pharmaceutically
20 acceptable salt thereof for the treatment of humans and other mammals it is
normally formulated in accordance with standard pharmaceutical practice as a
pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may
be administered in a standard manner for the treatment of the indicated diseases, for
25 example orally, parenterally, sub-lingually, transdermally, rectally, via inhalation or
via buccal administration.

- Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil,
- 5 olive oil, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine
- 10 encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.
- 15 Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.
- Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.
- 20 A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.
- 25 Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to themselves a single dose.

- Each dosage unit for oral administration contains suitably from 0.1 mg to 5 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 10 1.0% of a compound of Formula (I).

- The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a 15 compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.
- 20 No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

I. Binding Assay

5 A) **CHO cell membrane preparation.**

CHO cells stably transfected with human ET_A and ET_B receptors were grown in 245 mm x 245 mm tissue culture plates in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum. The confluent cells were washed with Dulbecco's phosphate-buffered saline containing a protease 10 inhibitor cocktail (5 mM EDTA, 0.5 mM PMSF, 5 ug/ml of leupeptin and 0.1 U/ml of aprotinin) and scraped in the same buffer. After centrifugation at 800 x g, the cells were lysed by freezing in liquid nitrogen and thawing on ice followed by homogenization (30 times using a glass dounce homogenizer) in lysis buffer containing 20 mM Tris HCl, pH 7.5, and the protease inhibitor cocktail. After an 15 initial centrifugation at 800 x g for 10 min to remove unbroken cells and nuclei, the supernatants were centrifuged at 40,000 x g for 15 min and the pellet was resuspended in 50 mM Tris HCl, pH 7.5, and 10 mM MgCl₂ and stored in small aliquots at -70°C after freezing in liquid N₂. Protein was determined by using the BCA method and BSA as the standard.

20 B) **Binding studies.**

[¹²⁵I]ET-1 binding to membranes prepared from CHO cells was performed following the procedure of Elshourbagy *et al.* (1993). Briefly, the assay was initiated in a 100 ul volume by adding 25 ul of [¹²⁵I]ET-1 (0.2-0.3 nM) in 0.05% BSA to membranes in the absence (total binding) or presence (nonspecific 25 binding) of 100 nM unlabeled ET-1. The concentrations of membrane proteins were 0.5 and 0.05 ug per assay tube for ET_A and ET_B receptors, respectively. The incubations (30°C, 60 min) were stopped by dilution with cold buffer (20 mM Tris HCl, pH 7.6, and 10 mM MgCl₂) and filtering through Whatman GF/C filters (Clifton, NJ) presoaked in 0.1% BSA. The filters were washed 3 times (5 ml each 30 time) with the same buffer by using a Brandel cell harvester and were counted by using a gamma counter at 75% efficiency.

The following examples are illustrative and are not limiting of the compounds of this invention.

5

EXAMPLE 1

(E)-alpha-[[1-n-Butyl-5-[2-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid

- 10 a) (E)-Ethyl 6-Methoxy-alpha-[(7-methoxy-4-oxo-4H-1-benzopyran-3-yl)methylene]-1,3-benzodioxole-5-propanoate

A solution of 3-formyl-7-methoxychromone (0.67 g, 3.3 mmol) and ethyl hydrogen 2-[(6-methoxy-3,4-methylenedioxy)benzyl]malonate (0.89 g, 3.0 mmol) in benzene (30 mL) was treated with piperidine (0.15 mL, 1.5 mmol) followed by

- 15 acetic acid (0.085 mL, 1.5 mmol). The reaction was stirred at reflux equipped with a Dean Stark apparatus for 2 h. The mixture was cooled then extracted with EtOAc (200 mL). The organic extract was washed successively with saturated NaHCO₃ and brine, dried (MgSO₄) and concentrated under vacuum. The resulting residue was purified by column chromatography (silica gel, EtOAc/hexane, gradient 75:25
20 to 70:30) to afford a material consisting of a 1.2 :1 mixture of E:Z enoates as an oil (1.02 g, 78%). Recrystallization of this material from ethanol affords the title compound as the E-isomer, exclusively.

Data for the the E-isomer: mp 140-141°C; MS (ESI) *m/z* 439 (M+H)⁺. Anal.

Calcd for C₂₄H₂₂O₈: C, 65.75; H, 5.06. Found: C, 65.56; H, 4.99.

25

- b) (E)-Ethyl alpha-[[1-Butyl-5-(2-hydroxy-4-methoxyphenyl)-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoate and (E)-Ethyl alpha-[[1-Butyl-3-(2-hydroxy-4-methoxyphenyl)-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoate

- 30 A solution of the compound of Example 1(a) (0.679 g, 1.55 mmol), butylhydrazine oxalate (0.552 g, 3.1 mmol) and sodium acetate trihydrate (1.265 g,

9.3 mmol) in a mixture of 9:1 EtOH:H₂O (31 mL) was stirred at reflux for 1 h. The reaction mixture was cooled and subsequently partitioned between EtOAc (300 mL) and aqueous pH 7 buffer. The organic extract was washed with brine, dried (Na₂SO₄) and concentrated under vacuum. The resulting residue was purified by column chromatography (silica gel, EtOAc/hexane, 60:40) to afford the 1,3,4-pyrazole (340 mg, 43%) followed by the isomeric 1,4,5-pyrazole (361 mg, 46%). Data for the 1,4,5-pyrazole: *Rf* (70:30 hexane:ethyl acetate) 0.14; ¹H NMR (400 MHz, CDCl₃) δ 0.79 (t, *J* = 7.3 Hz, 3 H), 1.12-1.21 (m, 2 H), 1.20 (t, *J* = 7.2 Hz, 3 H), 1.67 (quintet, *J* = 7.4 Hz, 2 H), 3.79 (s, 3 H), 3.83 (s, 3 H), 3.86-3.95 (m, 4 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 5.84 (s, 2 H), 6.53 (s, 1 H), 6.54 (s, 1 H), 6.56 (d, *J* = 2.4 Hz, 1 H), 6.61 (dd, *J* = 8.5, 2.4 Hz, 1 H), 7.03 (d, *J* = 8.5 Hz, 1 H), 7.39 (s, 1 H), 7.60 (s, 1 H); MS (ESI) *m/z* 509 (M+H)⁺. Data for 1,3,4-pyrazole: *Rf* (70:30 hexane:ethyl acetate) 0.41; ¹H NMR (400 MHz, CDCl₃) δ 0.91 (t, *J* = 7.3 Hz, 3 H), 1.22-1.25 (m, 2 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.80 (quintet, *J* = 7.4 Hz, 2 H), 3.76-3.81 (m, 2 H), 3.77 (s, 3 H), 3.78 (s, 2 H), 4.04 (t, *J* = 7.1 Hz, 2 H), 4.24 (q, *J* = 7.2 Hz, 2 H), 5.88 (s, 2 H), 6.49-6.54 (m, 1 H), 6.55 (s, 2 H), 6.61 (d, *J* = 2.5 Hz, 1 H), 7.32 (s, 1 H), 7.42 (d, *J* = 8.5 Hz, 1 H), 7.92 (s, 1 H), 10.5 (s, 1 H); MS (ESI) *m/z* 509 (M+H)⁺.

c) (*E*)-Ethyl *alpha*-[[1-Butyl-5-[4-methoxy-2-[[2-(methoxycarbonyl)phenyl]methoxy]phenyl]-1*H*-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoate

A solution of the 1,4,5-pyrazole of Example 1(b) (0.34 g, 0.67 mmol) in DMF (2.0 mL) was added dropwise to a slurry of NaH (0.024 g, 1.0 mmol) in DMF (1.3 mL) at room temperature. The reaction was stirred for 3 min at which time was added methyl 2-(bromomethyl)benzoate (0.23 g, 1.0 mmol) and stirring continued for 1 h at room temperature. The mixture was quenched with aqueous pH 7 buffer, then diluted with EtOAc. The organic extract was washed with brine, dried (Na₂SO₄) and concentrated under vacuum. The resulting residue was purified by column chromatography (silica gel, gradient hexane/Et₂O, 60:40 to 50:50) to

afford the title compound (396 mg, 90%). *Rf* (70:30 hexane:ethyl acetate) 0.23; MS (ESI) *m/z* 657 ($M+H$)⁺.

d) (*E*)-*alpha*-[[1-Butyl-5-[2-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-

5 pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic Acid

To a solution of the ester of Example 1(c) (0.396 g, 0.60 mmol) in MeOH (16.2 mL) was added aqueous LiOH•H₂O (0.253 g, 6.0 mmol, in 1.8 mL H₂O), and the reaction was heated at reflux for 4 h. After cooling to room temperature, acetic acid (2.5 mL) was added followed by H₂O (15 mL) at which time a precipitate formed. Most of the methanol was removed under reduced pressure, and the resulting aqueous solution was cooled to 0°C. The mixture was filtered and the precipitate was recrystallized from EtOAc (-20 °C) to give the title compound as white crystals (0.27 g). The mother liquors were purified by column chromatography (silica gel, gradient CH₂Cl₂/hexane/EtOAc/HOAc 40:40:20:1 to 15 40:30:30:1) to afford an additional 86 mg of title compound (356 mg, 96% overall): mp 213-214°C; *Rf* (50:50:1 hexane:ethyl acetate: acetic acid) 0.43; ¹H NMR (400 MHz, CDCl₃) δ 0.80 (t, *J* = 7.3 Hz, 3 H), 1.21-1.26 (m, 2 H), 1.69-1.77 (m, 2 H), 3.59 (s, 2 H), 3.81 (s, 3 H), 3.86 (s, 3 H), 3.97-4.02 (m, 2 H), 5.53 (s, 2 H), 5.82 (s, 2 H), 6.47 (s, 1 H), 6.52 (s, 1 H), 6.67 (dd, *J* = 8.4, 2.2 Hz, 1 H), 6.70 (d, *J* = 2.2 Hz, 20 1 H), 7.12 (d *J* = 8.4 Hz, 1 H), 7.32-7.36 (m, 2 H), 7.48 (t, *J* = 7.6 Hz, 1 H), 7.52 (s, 1 H), 7.54 (s, 1 H), , 8.08 (d, *J* = 7.4 Hz, 1 H); MS (ESI) *m/z* 613 ($M-H$)⁻. Anal. Calcd for C₃₄H₃₄N₂O₉ • 0.25 H₂O: C, 65.96; H, 5.62; N, 4.52. Found: C, 65.94; H, 5.44; N, 4.44.

25 Alternately 1-butyl-5-[2-(2-carboxyphenyl)methoxy]-4-methoxyphenylpyrazole-4-carboxyaldehyde may be prepared as follows.

a) (*E*)-Methyl 2-[[2-(3-hydroxy-1-oxo-2-propenyl)-5-methoxyphenoxy]methyl]benzoate

30 To a 12 L round bottomed flask, was added 60% sodium hydride (50.9 g, 1.27 mol, 2 equivalents). Toluene (600 mL) was added and the resulting solution

was stirred. Methyl 2-[(2-acetyl-5-methoxyphenoxy)methyl]benzoate (200.0 g, 0.636 mol) dissolved in toluene (2.0 L) was added slowly over a period of 20 minutes. After the addition was complete, the solution was stirred for a period of 15 minutes. Methyl formate (229.1 g, 235 mL, 3.82 mol) was added over 20 minutes.

- 5 The mixture was stirred for 1 hour at ambient temperature. Sodium methoxide (34.3 g, 0.636 mol) was added in three equal portions over 30 minutes. The mixture was stirred at ambient for 16 hours. HPLC of the reaction mixture showed the absence of starting material. Hexane (6 L) was added and the reaction mixture was stirred for 1 hour. The solids were filtered and washed with 2 L of hexane and 10 dried under vacuum (0.5 mTorr) to afford (E)-methyl 2-[[2-(3-hydroxy-1-oxo-2-propenyl)-5-methoxyphenoxy]methyl]benzoate, monosodium salt (303.9 g). The (E)-methyl 2-[[2-(3-hydroxy-1-oxo-2-propenyl)-5-methoxyphenoxy]methyl]benzoate, monosodium salt was slurried in water (3 L) and toluene (4 L) was added. A solution of 10% citric acid (2.5 L) was added and 15 the solution stirred for 1 hour. The layers were separated, and the aqueous layer was extracted with 2 L of toluene. The combined toluene layers were washed with brine solution (2 x 2 L) and dried (magnesium sulfate), filtered and concentrated to a solid which was triturated with hexane (2 L). The solid was filtered and dried to afford the title compound (188.4 g, 86.6% yield) as a light yellow solid: ¹H NMR 20 (300 MHz, CDCl₃) δ 8.20 (1H, d), 8.05 (1H, d), 7.95 (1H, m), 7.70 (1H, d), 7.65 (1H, m), 7.45 (1H, m), 6.50 (2H, m), 5.65 (2H, m), 5.3 (1H, br s), 3.90 (3H, s), 3.80 (3H, s).

- b) (E)-Methyl 2-[[2-[3-(diethylamino)-1-oxo-2-propenyl]-5-methoxyphenoxy]methyl]benzoate
25

To a 2 L round bottomed flask was added (E)-methyl 2-[[2-(3-hydroxy-1-oxo-2-propenyl)-5-methoxyphenoxy]methyl]benzoate (104 g, 0.304 mol) and 1 L of toluene. After complete dissolution, diethylamine (28.3g, 40 mL, 0.39 mol) was rapidly added under nitrogen via an addition funnel into the stirred solution. The 30 reaction mixture was stirred under nitrogen for 1 h and it was then concentrated under reduced pressure to give approximately 120 g (100% yield) of the title

compound as an orange solid: ^1H NMR (300 MHz, CDCl_3) δ 8.02 (1H, d), 7.84 (1H, d) 7.67 (2H, bd) 7.51 (1H, t) 7.35 (1H, t), 6.54 (2H, m), 5.75 (1H, d), 5.52 (2H, s), 3.80 (3H, s), 3.23 (4H, br), 1.14 (6H, br).

5 c) 1-Butyl-5-[2-(2-methoxycarbonylphenylmethoxy)-4-methoxyphenyl-1H-pyrazole

To a 5 L round bottomed flask was added (E)-methyl 2-[[2-[3-(diethylamino)-1-oxo-2-propenyl]-5-methoxyphenoxy]methyl]benzoate (150 g, 0.37 mol), 2.9 L of methanol and 0.45 L of water. After complete dissolution, a 10 premixed quantity of sodium acetate (294 g, 3.58 mol) and n-butylhydrazine oxalate salt (133 g, 0.746 mol) was added via a powder funnel in rapid portions over a period of 20 minutes. The reaction mixture was blanketed with nitrogen during the reaction period. After 20 hours the reaction mixture was partitioned between 3 L of ethyl acetate and 3 L of water. The aqueous was removed and 15 poured into 2 L of ethyl acetate and the aqueous was separated once again. This operation was repeated once more with 1.2 L of ethyl acetate (a total of 6 L of ethyl acetate used in total). The combined organic extracts were dried (magnesium sulfate) and concentrated under reduced pressure to 187 g of a thick oil. Flash chromatography (50% TBME/Hex) afforded the title compound (153 g, 73% yield) 20 as a colourless oil which slowly solidified on standing: ^1H NMR (300 MHz, CDCl_3) δ 8.02 (1H, d), 7.6 (1H, d), 7.52-7.22 (3H, m), 7.12 (1H, d), 6.64 (1H, d), 6.54 (1H, dd), 6.20 (1H, s), 5.48 (2H, s), 4.01 (2H, t), 3.89 (s 3H), 3.76 (3H, s), 1.7-1.5 (2H, m), 1.2-1.05 (2H, m), 0.7 (3H, t).

25 d) 1-Butyl-5-[2-(2-methoxycarbonylphenylmethoxy)-4-methoxyphenyl-1H-pyrazole-4-carboxyaldehyde

To a 2 L round bottomed flask was added 235 mL of DMF, followed by phosphorous oxychloride (125.0 g, 75 mL, 0.81 mol) under nitrogen. The temperature of the reaction mixture rose to 40 °C during the addition. The mixture 30 was then allowed to cool to room temperature and then was poured into a separate flask containing 235 mL of DMF and 1-butyl-5-[2-(2-

methoxycarbonylphenylmethoxy)-4-methoxyphenyl-1H-pyrazole (145 g, 0.36 mol). The resulting mixture was warmed to 95 °C under nitrogen; it was then allowed to cool and was poured into 1 L of water containing sodium acetate (100g, 1.13 mol). TBME (1.5 L) was added and the organic phase was separated. An 5 additional 1.5 L of TBME was added. The combined organic phases were dried with magnesium sulfate , filtered and concentrated to 200 g of crude product as a dark oil. Flash chromatography (30% TBME/hexane to 60% hex/TBME) afforded 100 g of solid which was recrystallized (TBME/ Hex) to give the title compound (91.3g, 58% yield) as a white solid: ^1H NMR (300 MHz, CDCl_3) δ 9.54 (1H, s), 10 8.1 (1H, s), 8.02 (1H, d), 7.45 (1H, t), 7.31 (1H, t), 7.29-7.261 (1H, m), 7.20 (1H, d), 6.71 (1H, s), 6.55 (1H, d), 5.5 (2H, s), 4.0 (2H, t), 3.92 (3H,s), 1.82-1.64 (2H, m), 1.22-1.08 (2H, m), 0.8 (3H, t).

e) 1-Butyl-5-[2-(2-carboxyphenyl)methoxy]-4-methoxyphenylpyrazole-4-
15 carboxyaldehyde

To a 2 L round bottomed flask equipped with an air driven stirrer and condenser was added 1-butyl-5-[2-(2-methoxycarbonylphenylmethoxy)-4-methoxyphenyl-1H-pyrazole-4-carboxyaldehyde (92 g, 0.218 mol), 0.883 L of methanol and lithium hydroxide (14.1 g, 0.336 moles, 1.54 eq). The mixture was 20 warmed to 70 °C and 0.222 L of water was added and the resultant light yellow mixture was maintained at 65 °C for 2 hours under nitrogen atmosphere. The solution was allowed to cool and then was concentrated under reduced pressure to give a thick oil. The oil was sequentially treated with citric acid (60 g, 0.285 moles, 1.3 eq) predissolved in 1.0 L of water and 1 L of dichloromethane. The 25 organic layer was removed and the aqueous layer was washed with 0.5 L of dichloromethane. The organic layers were combined, dried (magnesium sulfate), filtered through a pad of celite, and then concentrated under reduced pressure. This oil was redissolved in 0.8 L of toluene and placed in a -20 °C freezer for 12 hours. The solid formed was filtered, washed with 500 mL of toluene and placed in an 30 oven and dried to constant weight (1.0 Torr @ 50°C) to afford the title compound (72 g, 81% yield) as a white solid: ^1H NMR (300 MHz, CDCl_3) δ 9.55 (1H, s),

8.15-8.10 (2H, m), 7.51 (1H, t), 7.35 (1H, t), 7.28 (1H, d), 7.20 (1H, d), 6.70 (1H, s), 6.52 (1H, dd), 5.51 (2H, s), 4.1-3.90 (2H, m), 3.85 (3H, s), 1.82-1.64 (2H, m), 1.22-1.08 (2H, m), 0.8 (3H, t).

5

EXAMPLE 2(E)-alpha-[[1-n-Butyl-3-[2-[(2-carboxyphenyl)methoxy]4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid

- 10 a) (E)-Ethyl *alpha*-[[1-Butyl-3-[4-methoxy-2-[[2-(methoxycarbonyl)phenyl]methoxy]phenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoate

To a solution of the 1,3,4-pyrazole of Example 1(b) (0.23 g, 0.45 mmol) in DMF (5 mL) was added NaH (0.04 g, 1.83 mmol) at 0°C. The reaction stirred for 3 min at which time was added methyl 2-(bromomethyl)benzoate (0.22 g, 0.80 mmol) and stirring continued for 1.5 h at room temperature. The mixture was partitioned with EtOAc and 2% HCl, the resulting organic layer was then washed with water (2X). The aqueous layer was then neutralized with NaHCO₃ to pH 7 and then partitioned with EtOAc. The combined organic extract was washed with brine, dried (MgSO₄) and concentrated under vacuum. The resulting residue was purified by column chromatography (silica gel, gradient hexane/Et₂O, 67:33 to 65:35) to afford the title compound as an oil (0.25 g, 81%). ¹H NMR (400 MHz, CDCl₃) δ 0.91 (t, *J* = 7.4 Hz, 3 H), 1.13 (t, *J* = 7.1 Hz, 3 H), 1.30 (sextet, *J* = 7.4 Hz, 2 H), 1.83 (quintet, *J* = 7.4 Hz, 2 H), 3.73 (s, 2 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 3.89 (s, 3 H), 4.07 (q, *J* = 7.1 Hz, 2 H), 4.08 (t, *J* = 7.4 Hz, 2 H), 5.51 (s, 2 H), 5.87 (s, 2 H), 6.49 (s, 1 H), 6.59 (s, 1 H), 6.61 (dd, *J* = 8.4, 2.2 Hz, 1 H), 6.69 (d, *J* = 2.2 Hz, 1 H), 7.31 (t, *J* = 7.8 Hz, 1 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 7.39 (s, 1 H), 7.46 (t, *J* = 7.7 Hz, 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 7.70 (s, 1 H), 7.99 (d, *J* = 7.8 Hz, 1 H).

30

b) (*E*)-*alpha*-[[1-Butyl-3-[2-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl)methylene]-6-methoxy-1,3-benzodioxole-5-propanoic Acid

To a solution of the ester of example 2(a) (0.21 g, 0.33 mmol) in MeOH (13.5 mL) was added aqueous LiOH (0.13 g, 3.0 mmol, in 1.5 mL H₂O), and the reaction was heated at reflux for 5 h. To the mixture was added acetic acid (1 mL) and most of the solvent was removed under reduced pressure. The residue was partitioned between EtOAc and brine. The organic layer was dried (MgSO₄) and concentrated under vacuum. The resulting residue was purified by column chromatography (silica gel, CH₂Cl₂/EtOAc/hexane/HOAc, 40:30:30:1) to give a white solid, which was recrystallized from EtOAc to afford the title compound (0.175 g, 86%): mp 226-227 °C; ¹H NMR (400 MHz, CDCl₃) δ 0.94 (t, J = 7.3 Hz, 3 H), 1.33 (sextet, J = 7.3 Hz, 2 H), 1.85 (quintet, J = 7.3 Hz, 2 H), 3.44 (s, 2 H), 3.82 (s, 3 H), 3.85 (s, 3 H), 4.10 (t, J = 7.2 Hz, 2 H), 5.65 (s, 2 H), 5.85 (s, 2 H), 6.47 (s, 1 H), 6.57 (s, 1 H), 6.62 (dd, J = 8.4, 2.1 Hz, 1 H), 6.67 (d, J = 2.1 Hz, 1 H), 7.32-7.37 (m, 2 H), 7.43 (d J = 8.4 Hz, 1 H), 7.48-7.52 (m, 2 H), 7.76 (s, 1 H), 8.12 (d, J = 7.9 Hz, 1 H); MS (ESI) m/z 615 (M+H)⁺. Anal. Calcd for C₃₄H₃₄N₂O₉ • 0.25 H₂O: C, 65.97; H, 5.62; N, 4.52. Found: C, 65.84; H, 5.46; N, 4.31.

EXAMPLE 3

20

(E)-alpha-[[1-n-Butyl-5-[2-[(2-carboxyphenyl)methoxy]-5-chloro-4-methylphenyl]-1H-pyrazol-4-yl)methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid

25 a) (*E*)-Ethyl 6-Methoxy-*alpha*-[(6-chloro-7-methyl-4-oxo-4H-1-benzopyran-3-yl)methylene]-1,3-benzodioxole-5-propanoate

Following the procedure of Example 1(a), except substituting 6-chloro-3-formyl-7-methylchromone for 3-formyl-7-methoxychromone, the title compound was prepared in 38% yield: mp (hexane/ethyl acetate) 134-135 °C.

30

b) (*E*)-Ethyl *alpha*-[[1-Butyl-5-(5-chloro-2-hydroxy-4-methylphenyl)-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoate

Following the procedure of Example 1(b), except substituting the compound of Example 3(a) for (*E*)-ethyl 6-methoxy-*alpha*-[(7-methoxy-4-oxo-4H-1-benzopyran-3-yl)methylene]-1,3-benzodioxole-5-propanoate, the title compound was prepared in 41% yield: MS (ESI) *m/z* 527 (M+H)⁺.

c) (*E*)-Ethyl *alpha*-[[1-Butyl-5-[5-chloro-2-[(2-methoxycarbonyl)phenyl]methoxy]-4-methylphenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoate

Following the procedure of Example 1(c), except substituting the compound of Example 3(b) for (*E*)-ethyl *alpha*-[[1-butyl-5-(2-hydroxy-4-methoxyphenyl)-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propenoate, the title compound was prepared in 90% yield: MS (ESI) *m/z* 675 (M+H)⁺.

d) (*E*)-*alpha*-[[1-Butyl-5-[2-[(2-carboxyphenyl)methoxy]-5-chloro-4-methylphenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic Acid

Following the procedure of Example 1(d), except substituting the compound of Example 3(c) for (*E*)-ethyl *alpha*-[[1-butyl-5-[4-methoxy-2-[(2-methoxycarbonyl)phenyl]methoxy]phenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoate, the title compound was prepared in 83% yield. mp 114-116°C.

25

EXAMPLE 4

(E)-*alpha*-[[1-n-Butyl-5-[2-[(2-carboxyphenyl)methoxy]-4-chlorophenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid

110°C (dec)

EXAMPLE 5

(Z)-alpha-[[1-n-Butyl-5-[2-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid

188-189°C

5

EXAMPLE 6

(E)-alpha-[[1-Hydro-(3-[(2-Carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl)methylene]-6-methoxy-1,3-benzodioxole-5-propionic acid

10

EXAMPLE 7

(E)-alpha-[[1-Ethyl[5-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl)methylene]-6-methoxy-1,3-benzodioxole-5-propionic acid

15

(E)-alpha-[[1-Allyl-[5-(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl)methylene]-6-methoxy-1,3-benzodioxole-5-propionic acid

EXAMPLE 9

(E)-alpha-[[1-n-Butyl-5-[2-[(2-carboxyphenyl)methoxy]-4,5-dichlorophenyl]-1H-pyrazol-4-yl)methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid

226-228°C

20

(E)-alpha-[[1-n-Butyl-[3-[4-methoxy-2-[[N-(phenylsulfonyl)]carboxamido-methoxy]phenyl]-1H-pyrazol-4-yl)methylene]-6-methoxy-1,3-benzodioxole-5-propionic acid

EXAMPLE 11

(E)-3-[1-n-Butyl-5-[2-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(3,5-dimethoxyphenyl)methyl]-prop-2-enoic acid

EXAMPLE 12

(E)-alpha-[1-n-Butyl-5-[4-methoxy-2-[N-(phenylsulfonyl)]carboxamido-methoxy]phenyl]-1H-pyrazol-4-yl)methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid

5

EXAMPLE 13

(E)-3-[1-n-Butyl-5-[2-[2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(2,3-dimethoxyphenyl)methyl]-prop-2-enoic acid

188-189°C

10

EXAMPLE 14

(E)-3-[1-n-Butyl-5-[2-[2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(2,5-dimethoxyphenyl)methyl]-prop-2-enoic acid

192-194°C

15

EXAMPLE 15

(E)-alpha-[1-Benzyl-5-[2-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl)methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid

20

EXAMPLE 16

(E)-3-[1-n-Butyl-5-[2-[2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(2,6-dimethoxyphenyl)methyl]-prop-2-enoic acid

25

(E)-3-[1-n-Butyl-5-[2-[2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(2,5-dichlorophenyl)methyl]-prop-2-enoic acid

177-179°C

30

(E)-alpha-[1-n-Butyl-5-[2-[(2-hydroxymethylphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl)methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid

EXAMPLE 19

(E)-alpha-[1-n-Butyl-5-[2-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxan-5-propanoic acid

5 124-126°C

EXAMPLE 20

(E)-alpha-[5-[2-[(2-Carboxyphenyl)methoxy]-4-methoxyphenyl]-1-cyclopropyl-methyl-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid

10

EXAMPLE 21

(E)-3-[1-n-Butyl-5-[2-(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(2-methoxy-5-chlorophenyl)]-prop-2-enoic acid

202-203°C

15

EXAMPLE 22

(E)-3-[1-n-Butyl-5-[2-(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[2-chloro-5-methoxyphenyl]-prop-2-enoic acid

141-143°C

20

EXAMPLE 23

(E)-alpha-[1-n-Butyl-5-[2-[(2-Carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]methylene-2-chloro-5-thiophene propanoic acid

25

EXAMPLE 24

(E)-alpha-[1-n-Butyl-5-[2-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]methylene-3-indolepropanoic acid

EXAMPLE 25

(E)-3-[1-n-Butyl-5-[2-[2-(carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(2,4-dmethoxyphenyl)methyl]-prop-2-enoic acid

197-199°C

5

EXAMPLE 26

(E)-3-[1-n-Butyl-5-[2-(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(5-fluoro-2-methoxyphenyl)methyl]-prop-2-enoic acid

200-201°C

10

EXAMPLE 27

(E)-3-[1-n-Butyl-5-[2-(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(2-methoxy-5-nitrophenyl)methyl]-prop-2-enoic acid

239-241°C

15

EXAMPLE 28

(E)-3-[1-n-Butyl-5-[2-(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(2-methoxyphenyl)methyl]-prop-2-enoic acid

182-183°C

20

EXAMPLE 29

(E)-3-[1-n-Butyl-5-[2-(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(5-benzyloxy-2-methoxyphenyl)methyl]-prop-2-enoic acid

180-183°C

25

EXAMPLE 30

(E)-3-[1-n-Butyl-5-[2-(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(2-methoxyphenyl-5-methylthio)methyl]-prop-2-enoic acid

158-160°C

30

EXAMPLE 31

(E)-alpha-[[1-n-Butyl-5-[2-[(2-carboxyphenyl)methoxy]4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-2,4-dibromo-5-methoxybenzenepropanoic acid

5

EXAMPLE 32

(E)-alpha-[[1-n-Butyl-5-[2-[(2-carboxyphenyl)methoxy]4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-4-chloro-2,5-dimethoxybenzenepropanoic acid

EXAMPLE 33

- 10 (E)-alpha-[[1-(3-Butenyl)-5-[2-[(2-carboxyphenyl)methoxy]4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid

EXAMPLE 34

- 15 (E)-alpha-[[5-[2-[(2-Carboxyphenyl)methoxy]4-methoxyphenyl]-1-cyclopropyl-ethyl-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid

EXAMPLE 35

- 20 (E)-alpha-[[1-n-Butyl-5-[2-[N-(phenylsulfonyl)-(N-methyl)methylurea]4-methoxy-phenyl]-1H-pyrazol-4-yl]-methylen]-6-methoxy-1,3-benzodioxan-5-propanoic acid trifluoroacetate salt
58-60°C

EXAMPLE 36

- 25 (E)-alpha-[[1-n-Butyl-5-[2-(2-carboxyphenyl)methylether)-4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxan-5-propanoic acid
185-187°C

EXAMPLE 37

(E)-3-[1-n-Butyl-5-[2-(2-carboxyphenyl)methoxy-4-methoxyphenyl]-1,2,3-triazol-4-yl]-2-[(2-methoxy-4,5-methylenedioxy)phenylmethyl]-prop-2-enoic acid
m.p. 195°C.

5

EXAMPLE 38

(E)-3-[1-n-Butyl-5-[2-(2-hydroxymethyl)phenylmethoxy-4-methoxyphenyl]-1,2,3-triazol-4-yl]-2-[(2-methoxy-4,5-methylenedioxy)phenylmethyl]-prop-2-enoic acid
m.p. 134-137°C.

10

EXAMPLE 39

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

15

Inhalant Formulation

A compound of Formula I, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

20 Tablets/Ingredients Per Tablet

- | | | |
|----|---------------------------------------|-------|
| 1. | Active ingredient
(Cpd of Form. I) | 40 mg |
| 2. | Corn Starch | 20 mg |

<u>Tablets/Ingredients</u>	<u>Per Tablet</u>
3. Alginic acid	20 mg
4. Sodium Alginate	20 mg
5. Mg stearate	<u>1.3 mg</u>
5	2.3 mg

Procedure for tablets:

- Step 1 Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.
- Step 2 Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.
- Step 3 The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.
- Step 4 The wet granules are then dried in an oven at 140°F (60°C) until dry.
- 15 Step 5 The dry granules are lubricated with ingredient No. 5.
- Step 6 The lubricated granules are compressed on a suitable tablet press.

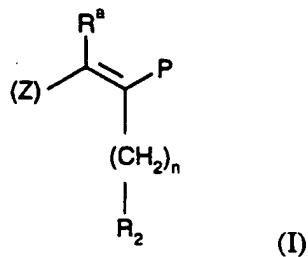
Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula I in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then sterilized by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

CLAIMS:

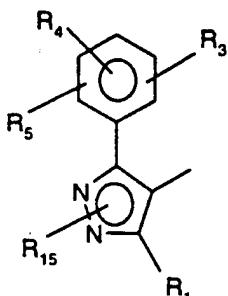
1. A compound of Formula (I):

5

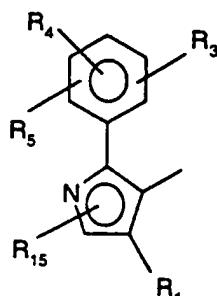


wherein (Z) is

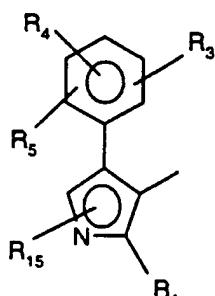
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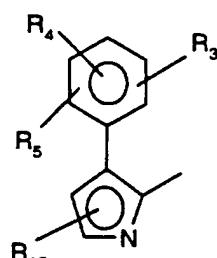
(d)



(e)

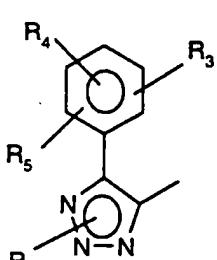


(f)

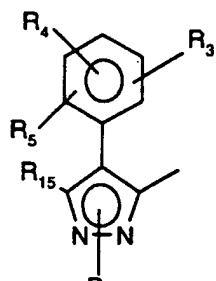


(g)

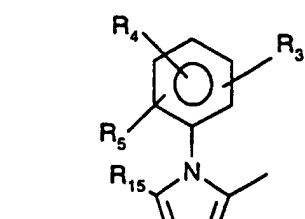
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(h)

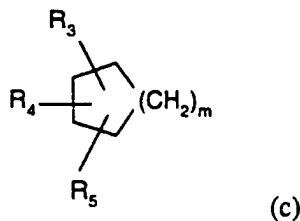


(i)



(j)

- P is tetrazol-5-yl, CO_2R_6 or $\text{C}(\text{O})\text{N}(\text{R}_6)\text{S}(\text{O})_q\text{R}_{10}$;
 R^a is independently hydrogen or C₁₋₆alkyl;
 R₁ is independently hydrogen, Ar, C₁₋₆alkyl, or C₁₋₆ alkoxy;
 5 R₂ is Ar, C₁₋₈alkyl, C(O)R₁₄ or



- R₃ and R₅ are independently R₁₃OH, C₁₋₈alkoxy, S(O)_qR₁₁, N(R₆)₂, NO₂, Br, F, I, Cl,
 10 CF₃, NHCOR₆, R₁₃CO₂R₇, -X-R₉-Y, -X(C(R₆)₂)OR₆, -(CH₂)_mX'R₈ or -
 X(CH₂)_nR₈ wherein each methylene group within -X(CH₂)_nR₈ may be
 unsubstituted or substituted by one or two -(CH₂)_nAr groups;
 R₄ is independently R₁₁, OH, C₁₋₅alkoxy, S(O)_qR₁₁, N(R₆)₂, Br, F, I, Cl or NHCOR₆,
 wherein the C₁₋₅alkoxy may be unsubstituted or substituted by OH, methoxy or
 15 halogen;
 R₆ is independently hydrogen or C₁₋₈alkyl;
 R₇ is independently hydrogen, C₁₋₁₀alkyl, C₂₋₁₀alkenyl or C₂₋₈alkynyl, all of which
 may be unsubstituted or substituted by one or more OH, N(R₆)₂, CO₂R₁₂, halogen or
 XC₁₋₁₀alkyl; or R₇ is (CH₂)_nAr;
 20 R₈ is independently R₁₁, CO₂R₇, CO₂C(R₁₁)₂O(CO)XR₇, PO₃(R₇)₂, SO₂NR₇R₁₁,
 NR₇SO₂R₁₁, CONR₇SO₂R₁₁, SO₃R₇, SO₂R₇, P(O)(OR₇)R₇, CN,
 CO₂(CH₂)_mC(O)N(R₆)₂, C(R₁₁)₂N(R₇)₂, C(O)N(R₆)₂, NR₇C(O)NR₇SO₂R₁₁,
 OR₆, or tetrazole which is substituted or unsubstituted by C₁₋₆alkyl;
 R₉ is independently a bond, C₁₋₁₀alkylene, C₁₋₁₀alkenylene, C₁₋₁₀alkyliidene, C₁₋₁₀alkynylene, all of which may be linear or branched, or phenylene, all of which may
 25 be unsubstituted or substituted by one or more OH, N(R₆)₂, COOH or halogen;
 R₁₀ is independently C₁₋₁₀alkyl, N(R₆)₂ or Ar;

R₁₁ is independently hydrogen, Ar, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, all of which may be unsubstituted or substituted by one or more OH, CH₂OH, N(R₆)₂ or halogen;

R₁₂ is independently hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₇alkynyl;

R₁₃ is independently divalent Ar, C₁₋₁₀alkylene, C₁₋₁₀alkylidene, C₂₋₁₀alkenylene, all 5 of which may be unsubstituted or substituted by one or more OH, CH₂OH, N(R₆)₂ or halogen;

R₁₄ is independently hydrogen, C₁₋₁₀alkyl, XC₁₋₁₀alkyl, Ar or XAr;

R₁₅ is independently hydrogen, Ar, C₁₋₆alkyl, or XAr;

R₁₆ is independently C₁₋₆alkyl or phenyl substituted by one or more C₁₋₆alkyl, OH, 10 C₁₋₅alkoxy, S(O)_qR₆, N(R₆)₂, Br, F, I, Cl, CF₃ or NHCOR₆;

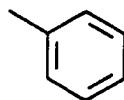
X is independently (CH₂)_n, O, NR₆ or S(O)_q;

X' is independently O, NR₆ or S(O)_q;

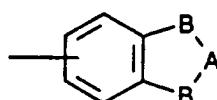
Y is independently CH₃ or X(CH₂)_nAr;

Ar is:

15



(a)



(b)

naphthyl, indolyl, pyridyl, thienyl, oxazolidinyl, thiazolyl, isothiazolyl, pyrazolyl,

20 triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, or pyrimidyl; all of which may be unsubstituted or substituted by one or more Z₁ or Z₂ groups;

A is independently C=O, or (C(R₆)₂)_m;

25 B is independently -CH₂- or -O-;

Z₁ and Z₂ are independently hydrogen, XR₆, C₁₋₈alkyl, (CH₂)_qCO₂R₆, C(O)N(R₆)₂, CN, (CH₂)_nOH, NO₂, F, Cl, Br, I, N(R₆)₂, NHC(O)R₆, O(CH₂)_mC(O)NR_aSO₂R₁₆, (CH₂)_mOC(O)NR_aSO₂R₁₆, O(CH₂)_mNR_aC(O)NR_aSO₂R₁₆ or tetrazolyl which may be substituted or unsubstituted by C₁₋₆alkyl, CF₃ or C(O)R₆;

30 m is independently 1 to 3;

- n is independently 0 to 6;
- q is independently 0, 1 or 2;
- provided R₃, R₄ and R₅ are not O-O(CH₂)_nAr or O-O R₆;
- and further provided that R₂ is not dihydrobenzofuran;
- 5 or a pharmaceutically acceptable salt thereof.
2. A compound of Formula (I) wherein P is CO₂R₆; R₁ is hydrogen; R₂ is Ar, cyclohexyl or C₁₋₄alkyl; R₃ and R₅ are independently hydrogen, CO₂R₆, OH, C₁₋₈alkoxy, C₁₋₈alkyl, N(R₆)₂, NO₂, Br, F, Cl, I, R₁₃CO₂R₇, X(CH₂)_nR₈, (CH₂)_mX'R₈, or X(C(R₆)₂)_mOR₆; R₄ is hydrogen, OH, C₁₋₅alkoxy, N(R₆)₂, Br, F, Cl, I, NHCOCH₃, or S(O)_q C₁₋₅alkyl wherein the C₁₋₅alkyl may be unsubstituted or substituted by OH, methoxy or halogen; R₆ is hydrogen, methyl or ethyl; R₇ is hydrogen, C₁₋₁₀alkyl, C₂₋₁₀alkenyl or C₂₋₈alkynyl, all of which may be unsubstituted or substituted by one or more OH, N(R₆)₂, CO₂R₁₂, halogen, or 15 R₇ is (CH₂)_nAr wherein n is zero or 1 and Ar is substituted phenyl; R₁₁ is hydrogen, phenyl, pyridyl all of which may be substituted or unsubstituted by one or two C₁₋₄alkyl groups; C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, all of which may be substituted or unsubstituted by one or more OH, CH₂OH, N(R₆)₂, or halogen; R₁₂ is hydrogen or C₁₋₆alkyl; R₁₃ is phenyl, pyridyl, or C₂₋₁₀alkylene, all of which 20 may be unsubstituted or substituted by one or more CO₂R₆, OH, CH₂OH, N(R₆)₂, or halogen; R₁₅ is hydrogen or C₁₋₆alkyl; and (Z) is (d).
3. A compound of claim 2 wherein P is CO₂H; R₁ is hydrogen; R₂ is a group Ar wherein Ar is a group (a) or (b) and in said group (a) or (b), Z₁ and Z₂ are 25 independently hydrogen, CO₂R₆, (CH₂)_nOH, C₁₋₄alkyl or C₁₋₆alkoxy and A is CH₂, and both Bs are O; R₃ is Br, Cl, C₁₋₈alkoxy or X(CH₂)_nR₈, wherein X is O, n is 0, 1, or 2, and R₈ is selected from: CO₂H, OH, tetrazolyl optionally substituted by C₁₋₈alkyl; CONR₇SO₂R₁₁ wherein R₇ is H or C₁₋₈alkyl, R₁₁ is C₁₋₈alkyl or phenyl optionally substituted by Br, Cl, F, C₁₋₈alkyl; or R₈ is phenyl or pyridyl 30 substituted by one or more Br, Cl, CO₂H, CH₂OH; R₅ is methoxy or N(R₆)₂ wherein R₆ is H or methyl; R₄ is hydrogen; R₆ is hydrogen, methyl or ethyl; R₇ is

hydrogen, C₁-10alkyl, C₂-10alkenyl or C₂-8alkynyl, all of which may be unsubstituted or substituted by one or more OH, N(R₆)₂, CO₂R₁₂, halogen, or R₇ is (CH₂)_nAr wherein R₇ is (CH₂)_nAr and n is zero or 1 and Ar is phenyl substituted or unsubstituted by halogen or C₁-5 alkoxy; R₁₁ is hydrogen,
5 phenyl, pyridyl wherein the phenyl or pyridyl be substituted or unsubstituted by one or two C₁-4alkyl groups; C₁-8alkyl, C₂-8alkenyl, C₂-8alkynyl, all of which may be substituted or unsubstituted by one or more OH, CH₂OH, N(R₆)₂, or halogen; R₁₂ is hydrogen or C₁-6alkyl; R₁₃ is phenyl, pyridyl, or C₂-10alkylene, all of which may be unsubstituted or substituted by one or more CO₂R₆, OH, CH₂OH, N(R₆)₂,
10 or halogen; R₁₅ is hydrogen, ethyl, isopropyl, n-butyl, cyclopropylmethyl or cyclopropylethyl; and (Z) is (d).

4. A compound of claim 1 selected from:

- (E)-alpha-[[5-[2-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1-ethyl-1H-pyrazol-4-yl]methylen]-6-methoxy-1,3-benzodioxole-5-propanoic acid;
15 (E)-alpha-[[1-Allyl-5-[2-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]methylen]-6-methoxy-1,3-benzodioxole-5-propanoic acid;

(E)-alpha-[[1-Butyl-5-[2-[(2-carboxyphenyl)methoxy]-4-chlorophenyl]-1H-pyrazol-4-yl]methylen]-6-methoxy-1,3-benzodioxole-5-propanoic acid;
20
(E)-alpha-[[1-Butyl-5-[4-methoxy-2-[[N-(phenylsulfonyl)]carboxamidomethoxy]phenyl]-1H-pyrazol-4-yl]methylen]-6-methoxy-1,3-benzodioxole-5-propanoic acid;
25
(E)-3-[1-Butyl-5-[2-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(2,5-dimethoxyphenyl)methyl]-prop-2-enoic acid;

30 (E)-alpha-[[1-Butyl-5-[2-[(2-hydroxymethylphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]methylen]-6-methoxy-1,3-benzodioxole-5-propanoic acid;

(E)-alpha-[[1-Butyl-5-[2-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-7-methoxy-1,4-benzodioxan-6-propanoic acid;

5 (E)-alpha-[[5-[2-[(2-Carboxyphenyl)methoxy]-4-methoxyphenyl]-1-cyclopropylmethyl-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid;

10 (E)-alpha-[[1-(3-Butenyl)-5-[2-[(2-hydroxymethylphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid;

15 (E)-alpha-[[5-[2-[(2-Carboxyphenyl)methoxy]-4-methoxyphenyl]-1-cyclopropylethyl-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid;

(E)-alpha-[[1-Butyl-5-[2-[(2-carboxyphenoxy)methyl]-4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid.

20 5. A compound of claim 1 which is (E)-alpha-[[1-Butyl-5-[2-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl]-1H-pyrazol-4-yl]methylene]-6-methoxy-1,3-benzodioxole-5-propanoic acid.

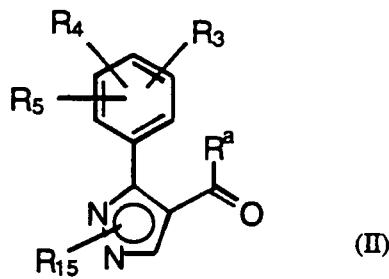
6. A compound of Claim 5 which is the disodium salt thereof.

7. A pharmaceutical composition comprising a compound of claim 1
25 and a pharmaceutically acceptable carrier.

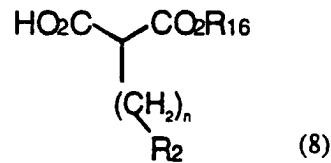
8. A compound of claim 1 for use as an endothelin receptor antagonist.

9. A method of treatment of diseases caused by an excess of endothelin comprising administering to a subject in need thereof, an effective amount of an endothelin receptor antagonist of Claim 1.

10. A method of treating renal failure or cerebrovascular disease which comprises administering to a subject in need thereof, an effective amount of a compound of Claim 1.
11. A method for the prophylaxis and treatment of radiocontrast induced 5 renal failure which comprises administering to a subject in need thereof, an effective amount of a compound of Claim 1.
12. A method of treatment of congestive heart failure which comprises administering to a subject in need thereof, an effective amount of a compound of Claim 1.
- 10 13. A method of treatment of unstable angina, coronary vasospasm and myocardial salvage which comprises administering to a subject in need thereof, an effective amount of a compound of Claim 1.
14. A method of preventing or treating restenosis which comprises administering to a subject in need thereof, an effective amount of a compound of 15 Claim 1.
15. A method of treatment of pulmonary hypertension which comprises administering to a subject in need thereof, an effective amount of a compound of Claim 1.
16. A method of treatment of stroke or subarachnoid hemorrhage which 20 comprises administering to a subject in need thereof, an effective amount of a compound of Claim 1.
17. A process for preparing a compound of Formula (Ia) by:
- (a) Reaction of a compound of Formula (II)



or a protected form or precursor thereof with a compound of Formula (8)



5 (wherein R₂ and R₁₆ are as defined in claim 1 for Formula (Id) hereinabove);

followed if necessary or desired by:

(b) conversion of one compound of Formula (Id) into a different compound of Formula (Id) e.g.

(i) when Formula (Id) contains a group CO₂R₆, CO₂R₇ or CO₂R₁₂

10 wherein R₆, R₇ or R₁₂ is alkyl, conversion to a corresponding compound where R₆, R₇ or R₁₂ represents hydrogen;

(ii) when Formula (Id) contains a hydroxy group (e.g. in R₃, R₄ or R₅) conversion to a different group, e.g. a group (CH₂)Ar where Ar is optionally substituted phenyl, by a method well known in the art; and/or

15 (c) salt formation.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/12661

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/415; C07D 405/02
US CL :514/406; 548/364.4

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,965,282 A (TAKAMURA ET AL.) 23 October 1990 (23/10/90), see column 1, lines 8-61.	4
A	US 3,703,513 (YAMAMOTO ET AL.) 21 November 1972 (21/11/72), see column 1, lines 16 to column 2, line 16.	4

<input type="checkbox"/>	Further documents are listed in the continuation of Box C.	<input type="checkbox"/>	See patent family annex.
* Special categories of cited documents:		"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*'A' document defining the general state of the art which is not considered to be of particular relevance		"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*'E' earlier document published on or after the international filing date		"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		*&	document member of the same patent family
*'O' document referring to an oral disclosure, use, exhibition or other means			
*'P' document published prior to the international filing date but later than the priority date claimed			

Date of the actual completion of the international search	Date of mailing of the international search report
18 SEPTEMBER 1996	15 OCT 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer R.W. RAMSUER <i>[Signature]</i> Telephone No. (703) 308-1235 <i>[Signature]</i>

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/12661

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 1-3, 5-17
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/12661

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

Of the multitude of variables and their permutations and combinations (e.g. Z, P, R1 through R16, Ar, X, X1 Y, A, B, Z1, Z2, etc. and the provisos) result in claimed subject matter that is so broad in scope that it is rendered virtually incomprehensible and thus no meaningful search can be given. Note also that the claimed subject matter lacks a significant structural element qualifying as the special technical feature that clearly defines a contribution over the prior art. The subject matter claimed contains a vinylene group which does not define a contribution over the prior art. There the first discernable invention as found in claim 4 (and the method of treating renal failure therewith) in claim 4 (and the method of treating renal failure therewith) has been searched.